Alkenyl Fischer Carbene Complexes and α,β-Unsaturated Imine Derivatives: Synthesis of Azepines and Mechanistic NMR Studies

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Dedicated to Professor Heinz Hoberg on the occasion of his 70th birthday

Abstract: 4-Amino-1-azadienes **1** react with α,β-unsaturated Fischer carbene complexes at −40 °C to give stereoselectively a variety of substituted 3*H*-4,5-dihydroazepines **3**; similarly, 1-hydroxy-1-azadienes (α,β-unsaturated oximes) **6** afforded the corresponding azepine derivatives **7**. Chiral, nonracemic carbene complexes **11** gave azepines **12**–**13** (d.e. = 40–44%) upon reaction with oxime **6a**; the major isomers were obtained in a diastereomerically and enantiomerically pure form (45–50% overall yield) after crystallization. An X-ray structure of **12a** allowed assignment of the absolute stereochemistry. The acid hydrolysis of azepines synthesized provided racemic and enantiomerically pure 1,6-dicarbonyl compounds (±)-**5**, (±)-**9**, and (−)-**14**, as well as diol (−)-**15**. The mechanism of the reaction of **1** and **2** was investigated by multinuclear (^{1}H, ^{13}C, ^{15}N, and ^{183}W) NMR characterization of four intermediates (**A**, **B**, **C**, and **D**) at low temperature. The experimental sequence of events involves: i) 1,2-nucleophilic addition of the unsubstituted imine nitrogen of **1** to the metal carbene function (zwitterion **A**, −60 °C), ii) cyclization to the seven-membered ring with 1,2-migration of the pentacarbonyl metal (zwitterion **B**, −40 °C), iii) reductive elimination and coordination of the metal to the amine nitrogen (intermediate **C**, −40 °C), and iv) thermal decomplexation and tautomerization (intermediate **D** and compound **3**, above −20 °C).

Keywords
azadienes · azepines · cycloadditions · Fischer carbenes complexes · reaction mechanisms

In the last decade transition metal Fischer carbene complexes have become a powerful tool in organic synthesis.[1] In particular, the cyclopropanation reaction of electron-poor and electron-rich alkenes has been the subject of numerous reports[2] and utilized in natural products synthesis as well; for instance, Wulff et al. have synthesized the prostaglandin PG2 in a short sequence consisting of the cyclopropanation of an enol ether with the appropriate dienylcarbene followed by ring expansion.[3] Subsequently, a variety of vinylcyclopropanes were prepared through the cyclopropanation reaction of 1,3-dienes.[4] A novel and interesting approach to racemic[5] and enantiomerically pure[6] seven-membered carbocycles based on this method has recently been reported; the process involves a combination of cyclopropanation of electron-rich dienes [X = CH(OMe), Y = $OSiMe_3$[5a] and X = CHR, Y = NR_2[5b, 6]] with chromium vinyl Fischer carbene complexes and [3,3] rearrangement of the resulting divinyl cyclopropane species (Fig. 1).[7]

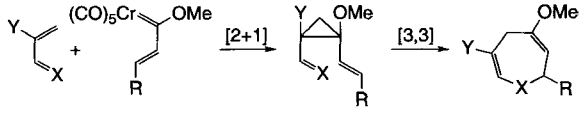

Fig. 1. [4 + 3] Annulation reaction of alkenyl chromium carbene complexes.

Because of our interest in medium-ring heterocycles[8] we thought of extending this sequence to nitrogen-containing substrates, for instance X = NR, which would be expected to yield azepines (Fig. 1). These nitrogen heterocycles are an extremely important class of compounds occurring in a range of natural and unnatural products; moreover, access to them is restricted to a very limited number of nongeneral methods of preparation.[9]

A literature search shows that the reaction of imines with Fischer carbene complexes has only been used in a limited number of cases. The most important work has been done by Hegedus et al., who developed an efficient, straightforward synthesis of β-lactams through the photochemical reaction of various types of imines with stabilized Group 6 carbene complexes.[10]

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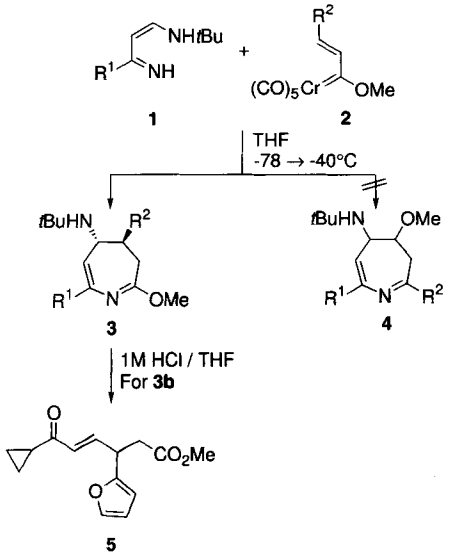
Regarding their thermal behavior towards carbene complexes, *N*-unsubstituted imines have been reported to undergo 1,2-[11] and 1,4-addition[12] to simple and α,β-unsaturated Fischer carbenes of Group 6, while simple *N*-methyl imines were found to condense with methyl substituted carbenes of chromium to furnish the corresponding α,β-unsaturated carbene complex.[11a] Moreover, Wulff et al.[13] found that chromium methoxycarbenes decompose when treated with simple imines, whereas the more reactive chromium and tungsten acyloxycarbenes yield products derived from metathesis and/or insertion of the imine function into the carbene carbon–oxygen bond. Therefore, the development of practical, synthetically useful routes involving the reaction of imine derivatives with transition metal carbene complexes still remains as a challenging goal.[14] We thought that employing α,β-unsaturated imine derivatives might result in a different reaction course; in fact, we have noted[15] that simple 1-azadienes smoothly undergo cyclopropanation at the carbon–carbon double bond followed by rearrangement to substituted pyrroles.

Accordingly, we have extended our research by studying the reactivity of α,β-unsaturated imine derivatives and alkenyl Fischer carbene complexes, and we disclose here a new synthesis of racemic and optically active azepines from 4-amino-1-azabutadienes[16] and from 1-hydroxy-1-azabutadienes.

Results and Discussion

Reaction of 4-amino-1-azabutadienes (1) with alkenyl chromium carbene complexes (2): We chose our most familiar nitrogen substrate, 4-amino-1-azabutadiene,[17] as the reagent to begin our studies into the reactions with carbene complexes. 3-Iminoprop-1-enylamines **1**, prepared by addition of the lithiated *N*-(*tert*-butyl)ethylideneamine to the corresponding nitrile R^1CN,[18] were mixed with chromium complexes **2** in THF at −78 °C. On warming to −40 °C over 3 h the mixture turned light brown, and the reaction went to completion. After treatment of the resulting mixture with silica gel and removal of the solvents, crude azepines **3** were isolated in excellent yields and with high purity. Compounds **3** were further purified by flash column chomatography (SiO_2, hexane/triethylamine 10:1) (Scheme 1, Table 1).



Scheme 1. [4 + 3] Cycloaddition of 4-amino-1-azadienes **1** with alkenyl chromium carbene complexes **2**.

Heterocycles **3** were formed as sole stereoisomers according to the ^1H NMR (300 MHz) data of the crude reaction mixture. The *trans* relationship of the substituents in **3** was deduced from NOE experiments. The regioisomeric [4 + 3] cycloadducts **4** were not detected in the crude reaction mixture. NMR experiments were used to establish that **3**, and not **4**, had been formed: the correlation of the methoxy hydrogen atoms with the most deshielded carbon atom in the 2D HMBC[19] spectrum rules out the structure **4**. On the other hand, the long-range connections derived from the aliphatic protons clearly establish the presence of a seven-membered ring in **3**.

The structure proposed was also confirmed by acid hydrolysis (Scheme 1); thus, treatment of the azepine **3b** (R^1 = *c*-C_3H_5; R^2 = 2-furyl) with diluted HCl followed by column chromatography afforded the expected ε-ketoester (*E*)-**5** ($^3J_{H-H}$ = 15.9 Hz) and minor amounts of the saturated *tert*-butylamino ketoester precursor.

Since two stereogenic centers are stereoselectively created in the reaction sequence, we decided to investigate the influence of a chiral auxiliary attached to either reagent on the stereochemical outcome of the cycloaddition. When the cycloaddition was attempted with aminoazadienes derived from (+)- and (−)-α-phenylethylamine in place of *tert*-butylamine, a complex mixture was formed from which no defined compounds could be identified. Furthermore, we found that the reaction of chiral carbene complexes derived from (+)- and (−)-menthol and from (−)-8-phenylmenthol with **1** was more sluggish than that of **2** and gave azepines **3** in lower yields, and with poor asymmetric induction (d.e.'s < 30%).

In summary, the reaction discussed above is unprecedented and offers an efficient and simple entry into substituted azepines in a regio- and stereoselective fashion. The great ease with which this [4 + 3] heterocyclization takes place (−78 to −40 °C) is remarkable. The major drawback appears to be the failure of the reaction when chiral azadienes or carbene complexes are employed.

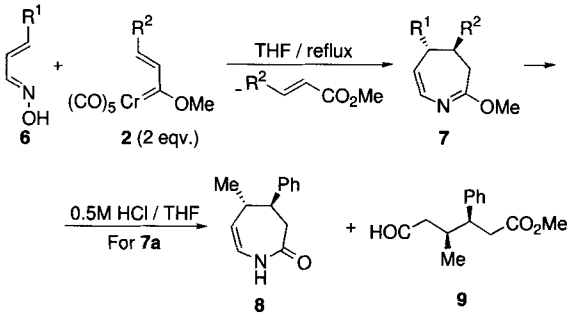
Table 1. Azepines **3** and **7** and hydrolysis products **5**, **8**, and **9** [a].

Product	R^1	R^2	*T*/h [b]	Yield [c]
3a	*c*-C_3H_5	Ph	3	90
3b	*c*-C_3H_5	2-furyl	3	80
3c	CH_3-CH_2	Ph	3	91
3d	4-CH_3-C_6H_4	2-furyl	3	62
3e	Ph	Ph	3	70
3f	4-Cl-C_6H_4	Ph	3	52
7a	CH_3	Ph	20	83
7b	CH_3	2-furyl	20	85
7c	Ph	Ph	44	57
7d	Ph	2-furyl	44	57
7e	(*E*)-1-Propenyl	2-furyl	65	52
5	–	–	3	75
8	–	–	1.5	32
9	–	–	1.5	64

[a] See Schemes 1 and 2. [b] **3** formed at −40 °C; **7** formed at reflux of THF; **5**, **8**, and **9** were formed by hydrolysis at 25 °C. [c] Isolated, not optimized yield.

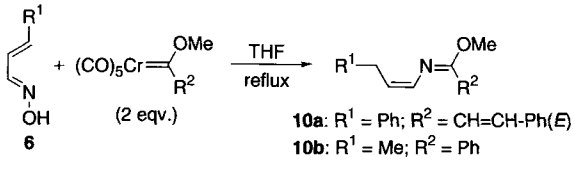
Reaction of 1-hydroxy-1-azabutadienes (6) with alkenyl chromium carbene complexes (2): Interestingly, the cycloaddition reaction of alkenyl Fischer carbene complexes with more common 1-azadiene derivatives such as α,β-unsaturated oximes was found to be successful. Thus, treatment of oximes **6** with vinylcarbenes **2** (molar ratio 1:2) in refluxing THF for 20–65 hours followed by stirring with SiO_2 resulted in the formation of azepines **7** of high purity; column chromatography of the crude

reaction mixture allowed the isolation of compounds **7** in moderate to good yields (52–85%). At least two equivalents of carbene had to be used, since one equivalent is required to remove the oxygen of the oxime functionality at some point during the reaction process. The reaction again proved to be stereoselective as only heterocycles **7** were detected in the crude reaction mixture (^{1}H NMR, 300 MHz); the *trans* stereochemical relationship was deduced from NOE experiments. Treatment of **7a** ($R^1 = CH_3$, R^2 = Ph) with 0.5 M HCl in THF resulted in the formation of azepinone **8** (32%) and formyl ester **9** (64%) (Scheme 2, Table 1).



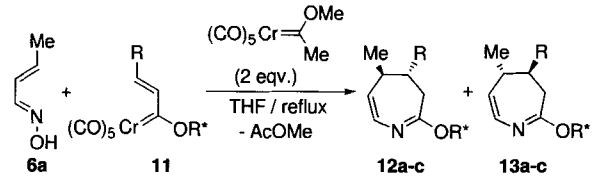
Scheme 2. [4 + 3] Cycloaddition of α,β-unsaturated oximes **6** with alkenyl chromium carbene complexes **2**.

The reaction of oxime **6b** (R^1 = Ph) and carbene complex **2** (R^2 = Ph) led to the azepine **7c** (57% yield, Table 1) along with compound **10a** (25% yield) resulting from coupling of the oxime nitrogen and the carbene carbon (Scheme 3). In the remaining examples, the corresponding azatrienes were only detected in the crude reaction mixture (<5%). This particular behavior of oximes was then confirmed by using simple carbenes; thus, the reaction of oxime **6a** (R^1 = Me) with (methoxybenzylidene)pentacarbonylchromium (molar ratio 1:2) in THF at reflux, followed by treatment with silica gel and column chromatography, furnished *N*-(1-butenyl)imidate **10b** in 85% yield along with 5–10% of the (*E*) isomer. The (*Z*) stereochemistry of the alkenyl moiety and the *anti* imidate geometry were established on the basis of the coupling constant ($^3J_{H-H}$ = 7.3 Hz) and NOE experiments, respectively.



Scheme 3. Formation of imidate derivatives **10** from α,β-unsaturated oximes and chromium Fischer carbene complexes.

We then turned to the reaction of **6** with chiral, nonracemic Fischer carbene complexes of chromium as outlined in Scheme 4. Thus, oxime **6a**, carbene complexes **11** (R = Ph, 2-furyl) derived from (−)-menthol,[20] and (1-methoxyethylidene)pentacarbonylchromium, which serves as the reducing agent,[21] in a molar ratio of 1:1:2 were refluxed in THF. The diastereoisomers **12a,b** and **13a,b** were obtained in a ratio of approximately 70:30 and in very high yields (87–90%), after purification by column chromatography. Significantly, the major diastereoisomers **12** were found to crystallize readily from methanol; this allowed us to isolate enantiomerically pure azepines **12a,b** (^{1}H NMR, 300 MHz) in about 50% overall yield from oxime **6a** (see Experimental Procedure). Conversely, carbene complex **11** (R = Ph) derived from (+)-menthol afforded a ca. 30:70 mixture of diastereomeric azepines **12c** and **13c** in 80% yield, which was crystallized as above to furnish pure azepine **13c** (45% overall yield from **6a**) (Scheme 4, Table 2).



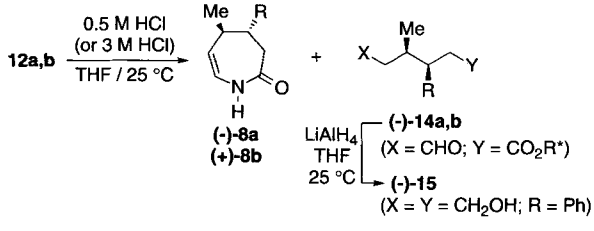
Scheme 4. [4 + 3] Cycloaddition of oxime **6a** with chiral, nonracemic carbene complexes **11** (**a**: R* = (1*R*,2*S*,5*R*)-menthyl, R = Ph; **b**: R* = (1*R*,2*S*,5*R*)-menthyl, R = 2-furyl; **c**: R* = (1*S*,2*R*,5*S*)-menthyl, R = Ph).

Table 2. Chiral, nonracemic azepines **12** and **13** from chiral, nonracemic carbene complexes **11**.

Entry	R	R*	12 + 13 Yield	12:13	Product	Isolated [a] Yield [b]	$[\alpha]_D^{20}$ (*c*) [c]
a	Ph	(1*R*,2*S*,5*R*)-menthyl	87	70:30	**12a**	50	+159.5 (0.19)
b	2-furyl	(1*R*,2*S*,5*R*)-menthyl	90	72:28	**12b**	48	+ 295.8 (0.59)
c	Ph	(1*S*,2*R*,5*S*)-menthyl	80	30:70	**13c**	45	−160.5 (0.18)

[a] By crystallization from methanol (d.e. >97%, ^{1}H NMR, 300 MHz). [b] Overall yield from **6a** or **11**. [c] Optical rotations were measured in CH_2Cl_2; *c* in g per 100 mL.

Hydrolysis of **12a** with 0.5 M HCl in THF yielded chiral azepinone (−)-**8a** (34%) and formyl ester (−)-**14a** (63%) with no signs of racemization; the latter was formed in 90% yield (<5% of **8a**) when the hydrolysis was carried out with 3 M HCl. In the same way, **12b** gave rise to (+)-**8b** and (−)-**14b** (Scheme 5, Table 3). The entire protocol formally represents the enantioselective Michael addition of ester homoenolates to α,β-unsaturated aldehydes, in which two chiral centers are created. We are aware of only a few reports on the synthesis of racemic



Scheme 5. Hydrolysis of chiral, nonracemic azepines **12**.

Table 3. Chiral, nonracemic azepines **8**, formyl esters **14**, and diol **15** from azepines **12**.

Product	R	R*	Yield (%) [a]	$[\alpha]_D^{20}$ (*c*) [b]
(−)-**8a**	Ph	–	34 (<5) [c]	−7.2 (0.61)
(−)-**14a**	Ph	(1*R*,2*S*,5*R*)-menthyl	63 (90) [c]	− 41.3 (0.155)
(+)-**8b**	2-furyl	–	32 (<5) [c]	+ 31.7 (0.265)
(−)-**14b**	2-furyl	(1*R*,2*S*,5*R*)-menthyl	59 (90) [c]	− 28.7 (0.275)
(−)-**15**	Ph	–	95	− 9.6 (0.595)

[a] Refers to isolated products. The e.e.'s and d.e.'s were >97% (HPLC or ^{1}H NMR, 300 MHz). [b] Optical rotations were measured in CH_2Cl_2; *c* in g per 100 mL. [c] Refers to hydrolysis with 0.5 M HCl. The yields in parentheses are for 3 M HCl hydrolysis.

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1,6-dicarbonyl compounds through 1,4-addition of homoenolates.[22, 23] Finally, the chiral auxiliary was efficiently removed by reduction of **14a** with $LiAlH_4$ at room temperature to give the chiral diol **15** in 95% yield.

An X-ray crystal structure analysis of **12a** confirmed the structure of the azepines obtained and provided their absolute configuration as well as those of subsequent derivatives.[24]

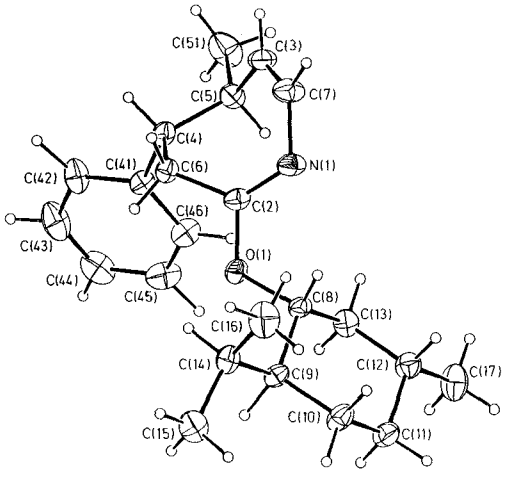
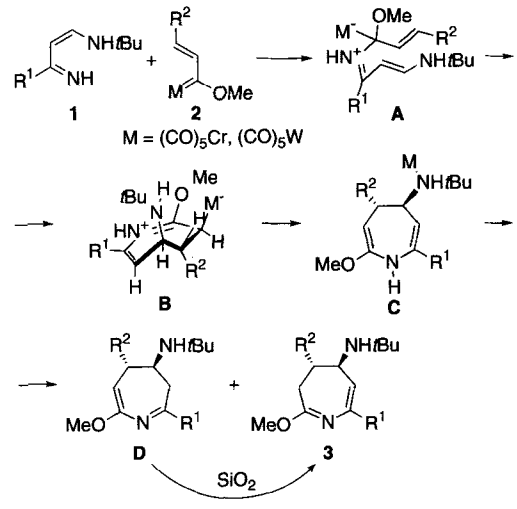


Fig. 2. Crystal structure of **12a**.

Although enantioselective syntheses based on chiral aminocarbene complexes are efficient and well known,[25] there are almost no examples involving their chiral alkoxy counterparts;[20] in fact, the procedure described here appears to be the first thermal cycloaddition using chiral alkoxycarbenes in which chiral centers are stereoselectively created.[26]

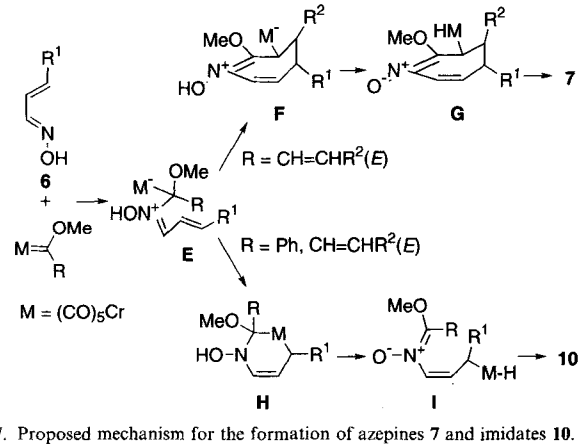
Proposed mechanism: The formation of seven-membered carbocycles is adequately rationalized in terms of tandem cyclopropanation/Cope rearrangement (see Fig. 1).[5, 6] In the case of aminoazadienes **1**, the tandem cyclopropanation of the enamine C=C bond/aza-Cope rearrangement does not explain the formation of azepines **3**, since such a sequence would lead to the formation of regioisomers **4** (see Scheme 1). On the other hand, the alternative cyclopropanation of the imine C=N bond, which is rather unlikely,[13] followed by Cope rearrangement would account for the regio- and stereochemistry of the azepines **3** obtained. However, the formation of azepines **7** from α,β-unsaturated oximes cannot be accomodated by this pathway, since it would give rise to azepines with a *cis* relationship between R^1 and R^2 (see Scheme 2). We now think that an ionic reaction pathway, evidence for which comes from NMR studies (see below), is more consistent with the results obtained from azadienes **1** and oximes **6** as well as with the reactivity trends of Fischer carbene complexes towards nucleophilic species (Scheme 6). Thus, nucleophilic attack of the unsubstituted nitrogen lone pair of amino azadiene **1** at the carbene carbon, a process previously postulated in the case of imines[13] and proven for azo derivatives[27] and keteneimines[28], would produce the zwitterion **A**, which is stabilized in a chairlike conformation where the two *trans* C=C bonds are in close proximity owing to electrostatic interactions. This arrangement of **A** favors the diastereoselective cyclization/[1,2]-$(CO)_5Cr$ shift to give intermediate **B**.[29] It should be noted that $(Z) \rightarrow (E)$ isomerization of the enamine moiety of **1** has to occur in order to account for the observed sterochemistry. Significantly, an analogous



Scheme 6. Proposed mechanism for the formation of azepines **3**.

structure derived from 1-propyl-4-phenyl-1-azabuta-1,3-diene and (1-methoxy-3-phenylprop-2-ynylidene)pentacarbonylchromium has just been isolated and its crystal structure determined.[30] The conformational flexibility of the seven-membered ring **B** would allow the metal to approach the *tert*-butylamine ligand; thus, the elimination of metal pentacarbonyl complex would be followed by metal coordination to the nitrogen to form intermediate **C**, which, upon thermally induced decomplexation, could produce conjugated azepines **D** and/or **3**. Finally, it was found that treatment with silica gel results in the exclusive isolation of the most stable imidate tautomer **3**.

A closely related pathway might explain the reaction of oximes **6** and carbene complexes **2** or **11** leading to azepines **7** or **12/13** (Scheme 7). The intermediates **E** and **F**, analoguous to **A**



Scheme 7. Proposed mechanism for the formation of azepines **7** and imidates **10**.

and **B**, are thought to be formed first; at this stage, **F** would undergo migration of the hydroxylic proton to the anionic metal center to generate nitrone **G**, which would be reduced by a second equivalent of carbene[31] and undergo reductive elimination to afford azepine **7**. Moreover, the formation of azatriene **10a** and azadiene **10b** is rationalized by assuming that the zwitterion **E** cyclizes through its anionic metal center to the metallacycle **H**. This process could be followed by ring reopening and hydrogen shift to generate the nitrone species **I**, which would give rise to compounds **10** after nitrone reduction and reductive elimination of the metal fragment.

NMR characterization of intermediates A–D: In order to gain evidence to support the proposed mechanism the reaction of aminoazadiene **1** (R^1 = cyclopropyl) with tungsten carbene **2** (metal = W; R^2 = 2-furyl) leading to the azepine **3b** was monitored by NMR spectroscopy (see Scheme 6).[32] For clarity the numbering of the atoms in all of the intermediates is based on that of the final azepine. Degassed [D_8]THF solutions of **1** and **2** (molar ratio 1:1) were mixed in a 5 mm NMR tube ($c \approx 0.5$ M) at −100 °C; at this temperature the ^{1}H and ^{13}C NMR spectra showed only unchanged starting materials.

Intermediate A (Fig. 3): Formation of the zwitterion **A** occurred slowly at −80 °C; the reaction went to completion within 20 min at −60 °C. The ^{13}C NMR spectrum[32] of **A** shows

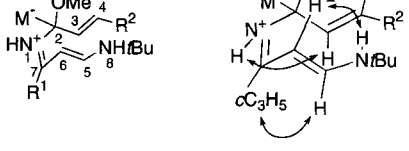


Fig. 3. Structure of **A**.

the C(2) and the methoxy carbon atoms at $\delta = 102.70$ [$^1J(^{13}C,^{183}W) = 71.6$ Hz] and 50.75, respectively, shifted significantly upfield with respect to the starting carbene complex ($\delta = 304.43$ and 71.34). All other signals appear at slightly modified chemical shifts and are easily assigned through the direct (HMQC[33]) and long-range (HMBC[19]) 2D ^{1}H,^{13}C heteronuclear correlation spectra. The metal carbonyl region exhibits the characteristic two W–CO signals for the $(CO)_5W$ moiety, and C(7) appears at $\delta = 166.51$. These data rule out a four-membered azametallacycle. The $^3J_{HH}$ coupling constants of 12.6 and 15.7 Hz, corresponding to C(5)=C(6) and C(3)=C(4), respectively, reveal that both the double bonds have an (*E*) configuration. The amine protons appear as relatively broad signals; the NH(8) proton is resolved into a doublet with a vicinal coupling of 14.5 Hz.

^{15}N NMR spectroscopy allowed us to define which nitrogen is actually bound to the former carbene carbon C(2). The 2D ^{1}H,^{15}N HMQC correlation map of **A** affords a chemical shift of $\delta = -204.9$ for N(1) and −228.7 for N(8) (Table 4). These values lie in the expected range for an iminium salt-type nitrogen[34] and an enamine nitrogen[35] considerably deshielded owing to the electron-withdrawing effect of the positively charged C(7)=N(1) group. NOE measurements permitted us to establish that **A** adopts a chairlike conformation in solution and to identify the unsubstituted nitrogen N(1) as the atom bonded to C(2). The most interesting cross-peaks found in the 2D ROESY are the correlations of NH(1) ($\delta = 8.53$) with H(3) ($\delta = 6.63$) and the peaks connecting the methoxy protons ($\delta = 2.84$) with H(6) ($\delta = 6.33$) and H(4) ($\delta = 5.54$). Additional dipolar correlations are indicated in Figure 3 by arrows. The bulky $(CO)_5W$ group is thus oriented equatorially, as expected, in order to minimize steric congestion. To the best of our knowledge this is the first characterization of the primary product resulting from the nucleophilic addition of an imine nitrogen to a Fischer carbene complex.

Intermediate B (Fig. 4): Compound **A** is thermally unstable[36] and disappears completely at −40 °C within 30 min leading to species **B** and **C** in a molar ratio of approximately 70:30. The ^{1}H NMR spectrum of the mixture measured in [D_8]THF shows substantial overlap of signals in the region of $\delta = 2.7$–4.0, which precludes structural studies. When CD_2Cl_2 was used as solvent[37] the relative **B**:**C** ratio was reversed, but the characterization of the intermediates could now be achieved.[32]

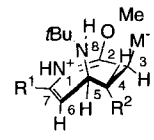


Fig. 4. Structure of **B**.

The ^{1}H NMR spectrum of zwitterion **B** shows four multiplets for the C–H protons of the azepine ring at $\delta = 3.05$ [H(3)], 3.12 [H(5)], 4.12 [H(4)], and 5.31 [H(6)]. The *trans*-diaxial arrangement for H(4) and H(5) is clearly supported by their coupling constant ($^3J_{H(4)H(5)} = 10.2$ Hz). The small coupling between H(3) and H(4) ($^3J_{H(3)H(4)} = 0.5$ Hz) means that the H(3)-C(3)-C(4)-H(4) dihedral angle is close to 90°. This condition is fulfilled when the seven-membered ring is in a boat conformation with the H(3) lying in a pseudoequatorial position. The tungsten atom is found to be attached to C(3) according to ^{183}W satellites observed at the base of H(3) [$\delta = 3.05$; $^2J(^1H^{183}W) = 6.2$ Hz by resolution enhancement processing of the spectrum].

Although no NH signals were identified in CD_2Cl_2, recording the ^{1}H NMR spectrum in [D_8]THF allowed us to assign NH(1) to the signal at $\delta = 9.76$, which was used in turn to determine $\delta_{N(1)}$ to be −252.4 from a 2D ^{1}H,^{15}N HMQC experiment.

2D ^{1}H,^{13}C correlation experiments (HMQC and HMBC pulse sequences) on **B** allowed the full assignment of the ^{13}C NMR spectrum (see Experimental Procedure). Notably, the signal for C(3) appears at $\delta = 26.23$ and shows ^{183}W satellites with a coupling constant $^1J(^{13}C,^{183}W) = 24.1$ Hz. In the HMBC spectrum, the ^{1}H,^{13}C connectivity of H(3) extends to the carbons separated by two or three bonds at $\delta = 200.4$, 176.36, 155.37, 57.97, and 52.75; these signals correspond to the four equivalent CO ligands [$^1J(^{13}C,^{183}W) = 129.9$ Hz], C(2), the *ipso* carbon of the furyl substituent, C(4), and C(5), respectively. Moreover, C(2) correlates with the methoxy protons, as does the *ipso* carbon of furyl with all the protons of the ring. The unambiguous assignment of C(4) and C(5) comes from the $^1J_{CH}$ correlation observed in the HMQC spectrum. One of the pieces of evidence that identifies C(6) ($\delta = 127.93$) and C(7) ($\delta = 134.53$) is based on the respective cross-peaks with H(4) and H(5) in the HMBC spectrum. The upfield shift of C(7) and the deshielding observed for C(6) relative to conventional enamine moieties[38] reflects a low enamine character of the C(6)=C(7) moiety.

Intermediate C (Fig. 5): As stated above compound **C** is formed at −40 °C (70% in CD_2Cl_2) along with **B**. The structural elucidation was carried out from the same data set used in the case of **B**. The ^{1}H NMR spectrum shows the four CH signals of the azepine ring at $\delta = 3.45$ [H(5)], 3.64 [H(4)], 3.84 [H(3)], and 4.35 [H(6)].[39] The ^{183}W satellites at the base of the singlet of NH(8) at $\delta = 3.0$ [$^2J(^1H(8)^{183}W) = 4.5$ Hz] confirm the presence of tungsten–nitrogen bonding. The ^{15}N chemical shifts are $\delta = -276.0$ [N(1)] and −319.8 [N(8)], assigned from a 2D ^{1}H,^{15}N HMQC correlation experiment; these values are in the expected range for sp^3 nitrogen atoms.[35]

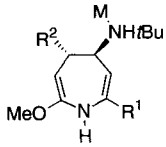


Fig. 5. Structure of **C**.

The coupling constant $^3J_{H(4)H(5)} = 8.8$ Hz is slightly less than the corresponding value for compound **B**, that is, the dihedral angle relating H(4) and H(5) is smaller in **C** than in **B**. Significantly, the olefin protons H(3) and H(6) are coupled to NH(1) ($^4J_{H(1)H(3)} = 2.3$, $^4J_{H(1)H(6)} = 2.8$ Hz). Long-range coupling across four bonds is favored when the coupled protons lie coplanar in a W arrangement. This condition is accomplished when

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the ring of the intermediate **C** is in a boat conformation with the (*tert*-butylamino)pentacarbonyltungsten group pseudoaxial.

*Compounds **D** and **3b*** (Fig. 6): When the temperature of the sample is raised to −20 °C the mixture of organometallic intermediates **B** and **C** cleanly transforms into a new mixture of two compounds **D** and **3b** within a period of 20 min. The NMR spectra[40] indicate that the 3*H*-4,5-dihydroazepine **3b** (2:1 ratio) is the final product isolated after treatment with silica gel when the reaction is carried out on a large scale, while structure **D** is the 4*H*-5,6-dihydroazepine tautomer. These assignments are deduced from the cross-peaks observed in the 2D HMBC spectrum of the mixture. The $^3J_{CH}$ correlations of the methoxy protons are key to the assignment of the quaternary carbon C(2) in both isomers. For compound **3b**, C(2) appears at $\delta = 175.65$ and correlates with the methylene protons of C(3) ($\delta = 2.65/2.77$), while C(2) in tautomer **D** resonates at $\delta = 156.71$. Furthermore, the methylene hydrogen atoms of **D** ($\delta = 2.27/2.46$) correlate with C(7) ($\delta = 193.10$). Straightforward analysis of the rest of the cross-peaks affords the full assignment of the ^{13}C NMR spectrum of each compound (see Experimental Procedure).

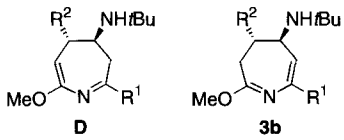

Fig. 6. Structure of **D** and **3b**.

The ^{15}N chemical shifts of N(1) ($\delta = -145.0$ and -185.4 for **D** and **3b**, respectively; Table 4) were deduced from the 2D $^1H,^{15}N$ HMBC spectrum through the correlations with the olefin protons and are characteristic for an sp^2-hybridized nitrogen. The values for N(8) could not be determined because the NH signals could not be identified in the ^1H NMR spectrum.

Table 4. ^{15}N and ^{183}W data of intermediates **A**–**D** and compounds **2** [M = W(CO)$_5$, R^2 = 2-furyl] and **3b**.

	δN(1)	δN(8)	δW
2 [a]			− 3002
A [b]	− 204.9	− 228.7	− 3007
B [c]	− 252.4		− 2896
C [c]	− 276.0	− 319.8	− 2875
D [d]	−145.0		
3b [d]	−185.4		

[a] At 25 °C in CD_2Cl_2. [b] At −80 °C in [D$_8$]THF. [c] At −80 °C in CD_2Cl_2. [d] At −80 °C in [D$_8$]THF.

^{183}W NMR Spectroscopy: The HMQC pulse sequence based on long-range $^1H,^{183}W$ couplings was applied in the characterization of the ^{183}W resonances in complexes **A**–**C** as well as in carbene **2**. This method[41] has proved to be successful even in tungsten complexes where the spin–spin coupling between the metal and the ligand is very small or even negligible.[42] Long-range $^1H,^{183}W$ correlations up to six bonds have recently been described.[43] In this way correlations through two and three bonds were observed for all compounds in less than 30 min. Zwitterion **A** also showed a four-bond interaction between H(4) and the metal. The results are summarized in Table 4.

The ^{183}W chemical shifts found ($\delta = -2875$ to -3007) lie in the known window for tungsten(0) complexes.[44] Interestingly, $\delta(^{183}W)$ of carbene **2** ($\delta = -3002$) is very similar to that of intermediate **A** ($\delta = -3007$), which again supports the zwitterionic structure of complex **A**. It is well known that tungsten carbene complexes bearing a donor heteroatom on the carbene carbon are actually best described by dipolar limiting forms of the type $^-W-C(R)=O^+-R'$.[45] Another interesting point is the small chemical shift difference between intermediates **B** and **C** ($\Delta\delta = 21$ ppm), where a carbon ligand is replaced with a nitrogen ligand, compared to that for compounds **A** and **B** ($\Delta\delta = 111$ ppm), which are more similar to each other.

Conclusions

An efficient [4 + 3] cycloaddition of 4-amino-1-azabutadienes and α,β-unsaturated oximes with Fischer carbene complexes leading to azepines, whose usefulness as both synthetic intermediates and therapeutic agents is well recognized,[9] is described. These are the first examples reported in which carbene complexes undergo [4 + 3] heterocyclization reactions. The synthesis of enantiomerically pure azepines is accomplished with more than acceptable chemical yields from oximes and chiral carbene complexes. The hydrolysis produces terminally differenciated bifunctional organic molecules. A mechanism based on the reactivity of azadienes, which is strongly supported by the ^1H, ^{13}C, ^{15}N, and ^{183}W NMR characterization of four intermediates, has been established in the case of 4-amino-1-azabutadienes. This is the first report on ^{183}W chemical shifts of Fischer carbenes and of the intermediate tungsten complexes formed in the course of a reaction.[46] The key step of the process is the diastereoselective and novel cyclization of an open-chain, conformationally stable precursor **A** to the seven-membered ring **B** with concomitant 1,2-migration of the pentacarbonylmetal fragment.

Experimental Procedure

General methods: All reactions involving organometallic species were carried out under a N_2 atmosphere. All common reagents and solvents were obtained from commercial suppliers and used without further purification unless otherwise indicated. THF was distilled from sodium benzophenone ketyl under a N_2 atmosphere prior to use. Hexane, ethyl acetate and triethylamine were distilled before use. TLC was performed on aluminum-backed plates coated with silica gel 60 with F_{254} indicator. Flash column chromatography was carried out on silica gel 60, 230–240 mesh. The enantiomeric purities were determined by chiral HPLC analysis using a Shimadzu instrument on a Chiralcel OD-H (Daicel Chem. Ind.) column (25 × 0.46 cm) and detection with photodiodide array UV/vis detector. Optical rotations were determined with a Perkin Elmer 241 polarimeter using a Na lamp; data are reported as follows: $[\alpha]_D^{20}$ (concentration in g per 100 mL, solvent). Melting points were obtained on a Büchi-Tottoli apparatus using open capillary tubes and are uncorrected. NMR spectra were run on Bruker AC 300 and AMX 400 spectrometer. The AC 300 was equipped with a 5 mm triple probe (^1H, ^{13}C, ^{31}P) and 90° pulses were 12.8 μs (^1H, 300 MHz) and 7 μs (^{13}C, 75 MHz). In the AMX 400 a 5 mm BB reverse probe head was used with the outer coil designed to work in the frequency range 18–162 MHz. Although at 9.4 T the ^{183}W resonance frequency is slightly outside the lower limit of the broad-band channel, it could be properly tuned, and reasonable pulse widths were obtained without additional frequency filtering. The 90° pulses and operating frequencies were: 10.4 μs (^1H, 400 MHz), 17.1 μs (^{15}N, 40.56 MHz), 14.5 μs (^{13}C, 100.61 MHz), 53 μs (^{183}W, 16.65 MHz). The attenuation levels used were 5 dB for the proton channel and 3 dB for the heteronuclei. The spectral references used were tetramethylsilane for ^1H and ^{13}C, and neat nitromethane for ^{15}N. $\delta(^{183}W)$ are referenced to the standard Na_2WO_4 taking into account $\Xi(Na_2{}^{183}WO_4) = 4.166404$ MHz and that under the experimental conditions used the resonance frequency of Me_4Si is 400.134661 MHz. Selected spectral parameters were as follows. $^1H,X$ 2D HMQC (X = ^{13}C, ^{15}N): spectral width, 4500 Hz in F2 and 22000/12000 Hz for $^{13}C/^{15}N$ in F1; 128 increments recorded; final matrix after zero filling, 2048 × 256; evolution delay of $^1J_{CH}$, 3.45 ms or $^1J_{NH}$, 5.56 ms; 16 scans per increment in F1. The same parameters were used for the corresponding ^1H, X 2D HMBC (X = ^{13}C, ^{15}N) spectra. In these experiments the number of scans was 32, and the evolution delay of $^nJ_{XH}$ was set to 60 ms. $^1H,^{183}W$ 2D HMQC: spectral width, 4500 Hz in F2 and 17000 Hz in F1; 64 increments recorded; final matrix after zero filling, 2048 × 256; evolution delay of $^nJ^{183}{}_{WH}$, 100 ms; 32 scans per increment in F1. Once observed the $\delta(^{183}W)$ a second experiment with a spectral window of 1000 Hz in F1 and 128 t_1 increments was performed in order to improve the digital resolution and to check for reflected signals. 2D ROESY: spectral width, 4500 Hz in both dimensions; 128 increments recorded; final matrix after zero filling, 2048 × 256; spin-lock mixing time 200 ms;

spin lock field $\gamma B_1/2\pi \approx 4.5$ kHz; 40 scans per increment in F1. All spectra were acquired in the TPPI mode, and a shifted sinus bell multiplication of $\pi/2$ in both dimensions prior to transformation was performed. High-resolution mass spectra were determined on a Finnigan MAT95 spectrometer.

General procedure for the synthesis of azepines 3: A solution of 4-amino-1-azadiene **1** (1.5 mmol) in THF (5 mL) was added to a solution of vinylcarbene **2** (1.5 mmol) in THF (40 mL) at −78 °C; the reaction mixture was allowed to reach −40 °C over 3 h, treated at room temperature with SiO_2 (3 g) for 3 h and filtered over Celite. The solvents were removed under vacuum and the residue subjected to column chromatography (SiO_2, hexane/NEt_3 10:1) furnishing pure cycloadducts **3**. Yields are given in Table 1.

***trans*-5-*tert*-Butylamino-7-cyclopropyl-2-methoxy-4-phenyl-4,5-dihydro-3*H*-azepine (3a)**: Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 0.35$ (m, 1H, CH_2), 0.55 (m, 2H, CH_2), 0.8 (s, 9H, $3 \times CH_3$), 0.85 (m, 1H, CH_2), 1.5 (m, 1H, CH), 2.2 (dd, $^2J(H,H) = 13.2$, $^3J(H,H) = 0.8$ Hz, 1H, CH_2), 2.8 (dd, $^2J(H,H) = 13.2$, $^3J(H,H) = 9.0$ Hz, 1H, CH_2), 3.25 (m, 1H, CH), 3.35 (dd, $^3J(H,H) = 11.6$, $^3J(H,H) = 4.5$ Hz, 1H, CH), 3.8 (s, 3H, CH_3), 5.35 (d, $^3J(H,H) = 4.5$ Hz, 1H, CH), 7.2–7.4 (m, 5H, CH_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 168.7$ (s), 145.8 (s), 143.3 (s), 128.5 (d), 127.3 (d), 127.0 (d), 117.8 (d), 60.1 (d), 55.0 (d), 53.1 (q), 50.5 (s), 35.3 (t), 29.3 (q), 15.5 (d), 4.5 (t) 3.6 (t); HRMS (70 eV, EI): calcd for $C_{20}H_{28}N_2O$ (M^+) 312.2201, found 312.2195.

***trans*-5-*tert*-Butylamino-7-cyclopropyl-4-(2-furyl)-2-methoxy-4,5-dihydro-3*H*-azepine (3b)**: Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 0.35$ (m, 1H, CH_2), 0.55 (m, 2H, CH_2), 0.8 (m, 1H, CH_2), 0.9 (s, 9H, $3 \times CH_3$), 1.5 (m, 1H, CH), 2.25 (dd, $^2J(H,H) = 12.5$, $^3J(H,H) = 1.3$ Hz, 1H, CH_2), 2.8 (dd, $^2J(H,H) = 12.5$, $^3J(H,H) = 8.6$ Hz, 1H, CH_2), 3.4 (m, 2H, $2 \times CH$), 3.75 (s, 3H, CH_3), 5.3 (d, $^3J(H,H) = 4.3$ Hz, 1H, CH), 6.15 (d, $^3J(H,H) = 3.4$ Hz, 1H, CH), 6.3 (m, 1H, CH), 7.35 (m, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 168.1$ (s), 156.6 (s), 146.1 (s), 141.1 (d), 117.3 (d), 110.0 (d), 105.7 (d), 53.3 (d), 53.1 (d), 53.0 (q), 50.8 (s), 33.6 (t), 29.3 (q), 15.6 (d), 4.5 (t) 3.7 (t); HRMS (70 eV, EI): calcd for $C_{18}H_{26}N_2O_2$ (M^+) 302.1994, found 302.2002.

***trans*-5-*tert*-Butylamino-7-ethyl-2-methoxy-4-phenyl-4,5-dihydro-3*H*-azepine (3c)**: Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 0.75$ (s, 9H, $3 \times CH_3$), 1.0 (t, $^3J(H,H) = 7.7$ Hz, 3H, CH_3) 2.15 (m, 2H, CH_2), 2.25 (d, $^2J(H,H) = 12.9$ Hz, 1H, CH_2), 2.85 (dd, $^2J(H,H) = 12.9$, $^3J(H,H) = 9.0$ Hz, 1H, CH_2), 3.25 (dd, $^3J(H,H) = 11.6$, $^3J(H,H) = 9.0$ Hz, 1H, CH), 3.4 (dd, $^3J(H,H) = 11.6$, $^3J(H,H) = 4.7$ Hz, 1H, CH), 3.9 (s, 3H, CH_3), 5.3 (d, $^3J(H,H) = 4.7$ Hz, 1H, CH), 7.1–7.4 (m, 5H, CH_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 168.0$ (s), 147.5 (s), 143.3 (s), 128.5 (d), 127.3 (d), 127.1 (d), 118.5 (d), 60.0 (d), 54.8 (d), 53.1 (q), 50.5 (s), 35.4 (t), 29.3 (q), 29.0 (t), 12.1 (q) ; HRMS (70 eV, EI): calcd for $C_{19}H_{28}N_2O$ (M^+) 300.2202 , found 300.2184.

***trans*-5-*tert*-Butylamino-4-(2-furyl)-2-methoxy-7-(4-methylphenyl)-4,5-dihydro-3*H*-azepine (3d)**: Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 0.85$ (s, 9H, $3 \times CH_3$), 2.25 (s, 3H, CH_3), 2.3 (d, $^2J(H,H) = 12.9$ Hz, 1H, CH_2) 2.8 (dd, $^2J(H,H) = 12.9$, $^3J(H,H) = 9.0$ Hz, 1H, CH_2), 3.4 (m, 1H, CH), 3.5 (dd, $^3J(H,H) = 11.6$, $^3J(H,H) = 4.7$ Hz, 1H, CH), 3.9 (s, 3H, CH_3), 5.95 (d, $^3J(H,H) = 4.7$ Hz, 1H, CH), 6.15 (d, $^3J(H,H) = 3.4$ Hz, 1H, CH), 6.25 (m, 1H, CH), 7.05 (d, $^3J(H,H) = 8.2$ Hz, 2H, CH_{arom}), 7.3 (m, 1H, CH), 7.45 (d, $^3J(H,H) = 8.2$ Hz, 2H, CH_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 168.6$ (s), 156.2 (s), 143.5 (s), 141.4 (d), 137.2 (s), 135.0 (s), 128.8 (d), 124.8 (d), 119.5 (d), 110.0 (d), 106.1 (d), 53.9 (d), 53.5 (q), 52.8 (d), 50.8 (s), 33.6 (t), 29.3 (q), 21.0 (q); HRMS (70 eV, EI): calcd for $C_{22}H_{28}N_2O_2$ (M^+) 352.2151, found 352.2160.

***trans*-5-*tert*-Butylamino-2-methoxy-4,7-diphenyl-4,5-dihydro-3*H*-azepine (3e)**: Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 0.8$ (s, 9H, $3 \times CH_3$), 2.3 (d, $^2J(H,H) = 13.1$ Hz, 1H, CH_2), 2.9 (dd, $^2J(H,H) = 13.1$, $^3J(H,H) = 9.2$ Hz, 1H, CH_2), 3.4 (dd, $^3J(H,H) = 11.8$, $^3J(H,H) = 9.2$ Hz, 1H, CH), 3.6 (dd, $^3J(H,H) = 11.8$, $^3J(H,H) = 4.8$ Hz, 1H, CH), 4.0 (s, 3H, CH_3), 6.15 (d, $^3J(H,H) = 4.8$ Hz, 1H, CH), 7.2–7.4 (m, 8H, CH_{arom}), 7.65 (m, 2H, CH_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 169.3$ (s), 143.1 (s), 142.9 (s), 137.8 (s), 128.7 (d), 128.1 (d), 127.4 (d), 127.3 (d), 124.9 (d), 120.8 (d), 59.7 (d), 55.6 (d), 53.5 (q), 50.6 (s), 35.4 (t), 29.3 (q); HRMS (70 eV, EI): calcd for $C_{23}H_{28}N_2O$ (M^+) 348.2202, found 348.2196.

***trans*-5-*tert*-Butylamino-7-(4-chlorophenyl)-2-methoxy-4-phenyl-4,5-dihydro-3*H*-azepine (3f)**: Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 0.8$ (s, 9H, $3 \times CH_3$), 2.35 (d, $^2J(H,H) = 13.3$ Hz, 1H, CH_2), 2.9 (dd, $^2J(H,H) = 13.3$, $^3J(H,H) = 9.7$ Hz, 1H, CH_2), 3.4 (dd, $^3J(H,H) = 12.1$, $^3J(H,H) = 9.7$ Hz, 1H, CH), 3.55 (dd, $^3J(H,H) = 12.1$, $^3J(H,H) = 4.7$ Hz, 1H, CH), 4.0 (s, 3H, CH_3), 6.15 (d, $^3J(H,H) = 4.7$ Hz, 1H, CH), 7.2–7.4 (m, 7H, CH_{arom}), 7.55 (d, $^3J(H,H) = 8.6$ Hz, 2H, CH_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 169.6$ (s), 142.7 (s), 142.2 (s), 136.3 (s), 133.1 (s), 128.7 (d), 128.2 (d), 127.3 (d), 126.2 (d), 121.2 (d), 59.6 (d), 55.6 (d), 53.6 (q), 50.6 (s), 35.4 (t), 29.8 (q); HRMS (70 eV, EI): calcd for $C_{23}H_{27}ClN_2O$ (M^+) 382.1812, found 382.1807.

Hydrolysis of dihydroazepine (3b): A solution of azepine **3b** (150 mg) in THF (30 mL) was treated with 1M HCl (30 mL) for 3 h. The resulting mixture was extracted with diethyl ether (3 × 20 mL), washed with sodium hydrogen carbonate, and dried with anhydrous sodium sulfate. Removal of the solvents followed by column chromatography (SiO_2; hexane/AcOEt 5:1) gave 90 mg of ε-ketoester **5** (75% yield) (Table 1).

Methyl 6-cyclopropyl-3-(2-furyl)-6-oxo-4-hexenoate (5): Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 0.9$ (m, 2H, CH_2), 1.05 (m, 2H, CH_2), 2.1 (m, 1H, CH), 2.75 (dd, $^2J(H,H) = 15.9$, $^3J(H,H) = 8.2$ Hz, 1H, CH_2), 2.85 (dd, $^2J(H,H) = 15.9$, $^3J(H,H) = 6.9$ Hz, 1H, CH_2), 3.65 (s, 3H, CH_3), 4.1 (q, $^3J(H,H) = 7.3$ Hz, 1H, CH), 6.1 (m, 1H, CH), 6.2 (d, $^3J(H,H) = 15.9$ Hz, 1H, CH), 6.3 (m, 1H, CH), 6.85 (dd, $^3J(H,H) = 15.9$, $^3J(H,H) = 7.3$ Hz, 1H, CH), 7.35 (m, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 199.9$ (s), 171.1 (s), 153.1 (s), 143.4 (d), 141.9 (d), 130.8 (d), 110.2 (d), 106.0 (d), 51.8 (q), 37.8 (d), 37.1 (t), 19.0 (d), 11.4 (q); HRMS (70 eV, EI): calcd for $C_{14}H_{16}O_4$ (M^+) 248.1049, found 248.1046.

General procedure for the synthesis of azepines 7: A solution of vinylcarbene **2** (2 mmol) and oxime **6** (1 mmol) in THF (50 mL) was refluxed (20–65 h, see Table 1) under nitrogen. The resulting mixture was allowed to cool to room temperature, stirred with SiO_2 (3 g) for 3 h, and filtered over Celite. Removal of solvents under vacuum followed by column chromatography (SiO_2, hexane/AcOEt/NEt_3 10:1:1) led to cycloadducts **7**. Yields are given in Table 1. In the case of $R^1 = R^2 = Ph$, imidate **10a** was isolated in 25% yield (see below).

***trans*-2-Methoxy-5-methyl-4-phenyl-4,5-dihydro-3*H*-azepine (7a)**: Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 0.9$ (d, $^3J(H,H) = 6.9$ Hz, 3H, CH_3), 2.5 (dd, $^2J(H,H) = 13.3$, $^3J(H,H) = 4.3$ Hz, 1H, CH_2), 2.55 (m, 1H, CH), 2.85 (dd, $^2J(H,H) = 13.3$, $^3J(H,H) = 6.4$ Hz, 1H, CH_2), 3.05 (m, 1H, CH), 3.8 (s, 3H, CH_3), 5.3 (dd, $^3J(H,H) = 8.4$, $^3J(H,H) = 4.9$ Hz, 1H, CH), 6.5 (dd, $^3J(H,H) = 8.4$, $^4J(H,H) = 1.9$ Hz, 1H, CH), 7.1–7.5 (m, 5H, CH_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 169.0$ (s), 145.3 (s), 134.6 (d), 128.4 (d), 127.1 (d), 126.5 (d), 123.5 (d), 57.1 (d), 53.2 (q), 38.9 (d), 37.6 (t), 19.4 (q); HRMS (70 eV, EI): calcd for $C_{14}H_{17}NO$ (M^+) 215.1310, found 215.1314.

***trans*-4-(2-Furyl)-2-methoxy-5-methyl-4,5-dihydro-3*H*-azepine (7b)**: Yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.0$ (d, $^3J(H,H) = 6.9$ Hz, 3H, CH_3), 2.4 (dd, $^2J(H,H) = 13.2$, $^3J(H,H) = 4.0$ Hz, 1H, CH_2), 2.55 (m, 1H, CH), 2.8 (dd, $^2J(H,H) = 13.2$, $^3J(H,H) = 6.4$ Hz, 1H, CH_2), 3.2 (m, 1H, CH), 3.7 (s, 3H, CH_3), 5.2 (dd, $^3J(H,H) = 8.2$, $^3J(H,H) = 5.0$ Hz, 1H, CH), 6.1 (d, $^3J(H,H) = 3.0$ Hz, 1H, CH), 6.3 (m, 1H, CH), 6.4 (dd, $^3J(H,H) = 8.2$, $^4J(H,H) = 2.2$ Hz, 1H, CH), 7.3 (m, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 168.7$ (s), 157.7 (s), 141.0 (d), 135.2 (d), 122.7 (d), 109.9 (d), 104.5 (d), 53.2 (q), 50.8 (d), 35.9 (d), 35.5 (t), 19.6 (q); HRMS (70 eV, EI): calcd for $C_{12}H_{15}NO_2$ (M^+) 205.1103, found 205.1112.

***trans*-2-Methoxy-4,5-diphenyl-4,5-dihydro-3*H*-azepine (7c)**: Yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 2.75$ (dd, $^2J(H,H) = 13.3$, $^3J(H,H) = 5.4$ Hz, 1H, CH_2), 2.95 (dd, $^2J(H,H) = 13.3$, $^3J(H,H) = 5.2$ Hz, 1H, CH_2), 3.45 (m, 1H, CH), 3.6 (ddd, $^3J(H,H) = 11.2$ Hz, $^3J(H,H) = 4.9$, $^4J(H,H) = 2.1$ Hz, 1H, CH), 3.8 (s, 3H, CH_3), 5.5 (dd, $^3J(H,H) = 8.9$, $^3J(H,H) = 5.1$ Hz, 1H, CH), 6.55 (dd, $^3J(H,H) = 8.9$, $^4J(H,H) = 2.1$ Hz, 1H, CH), 6.9–7.2 (m, 10H, CH_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 168.9$ (s), 144.5 (s), 143.4 (s), 135.0 (d), 128.2 (d), 128.1 (d), 128.0 (d), 127.1 (d), 126.4 (d), 126.2 (d), 121.4 (d), 56.7 (d), 53.4 (q), 52.6 (d), 37.4 (t); HRMS (70 eV, EI): calcd for $C_{19}H_{19}NO$ (M^+) 277.1467, found 277.1476.

***trans*-4-(2-Furyl)-2-Methoxy-5-phenyl-4,5-dihydro-3*H*-azepine (7d)**: Yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 2.6$ (dd, $^2J(H,H) = 13.7$, $^3J(H,H) = 4.7$ Hz, 1H, CH_2), 2.85 (dd, $^2J(H,H) = 13.7$, $^3J(H,H) = 5.4$ Hz, 1H, CH_2), 3.35–3.8 (m, 2H, $2 \times CH$), 3.7 (s, 3H, CH_3), 5.35 (dd, $^3J(H,H) = 8.6$ Hz and $^3J(H,H) = 5.1$ Hz, 1H, CH), 5.8 (m, 1H, CH), 6.1 (m, 1H, CH), 6.45 (dd, $^3J(H,H) = 8.6$, $^4J(H,H) = 2.2$ Hz, 1H, CH), 7.0–7.2 (m, 6H, CH_{arom}, CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 168.4$ (s), 156.4 (s), 143.4 (s), 141.0 (d), 135.3 (d), 128.2 (d), 127.9 (d), 126.4 (d), 120.4 (d), 109.8 (d), 105.2 (d), 53.3 (q), 50.0 (d), 48.5 (d), 35.5 (t); HRMS (70 eV, EI): calcd for $C_{17}H_{17}NO_2$ (M^+) 267.1259, found 267.1255.

***trans*-4-(2-Furyl)-2-Methoxy-5-(*E*-1-propenyl)-4,5-dihydro-3*H*-azepine (7e)**: Yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.6$ (d, $^3J(H,H) = 4.1$ Hz, 3H, CH_3), 2.55 (dd, $^2J(H,H) = 13.3$, $^3J(H,H) = 4.8$ Hz, 1H, CH_2), 2.80 (dd, $^2J(H,H) = 13.3$, $^3J(H,H) = 5.4$ Hz, 1H, CH_2), 3.15 (m, 1H, CH), 3.35 (m, 1H, CH), 3.7 (s, 3H, CH_3), 5.3 (dd, $^3J(H,H) = 8.5$, $^3J(H,H) = 5.1$ Hz, 1H, CH) 5.35 (m, 2H, $2 \times CH$), 6.05 (m, 1H, CH), 6.3 (m, 1H, CH), 6.45 (dd, $^3J(H,H) = 8.5$, $^4J(H,H) = 1.9$ Hz, 1H, CH), 7.3 (m, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 168.3$ (s), 157.0 (s), 141.0 (d), 135.0 (d), 132.2 (d), 126.5 (d), 120.0 (d), 109.9 (d), 104.9 (d), 53.2 (q), 47.9 (d), 44.4 (d), 35.2 (t), 17.9 (q); HRMS (70 eV, EI): calcd for $C_{14}H_{17}NO_2$ (M) 231.1259, found 231.1268.

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Hydrolysis of dihydroazepine 7a: A solution of azepine **7a** (0.5 mmol) in THF (30 mL) was treated with 0.5 M HCl (30 mL) for 1.5 h. The resulting mixture was extracted with diethyl ether (3 × 20 mL), washed with sodium hydrogen carbonate and dried with anhydrous sodium sulfate. Removal of the solvents followed by column chromatography (SiO_2; hexane/AcOEt 2:1) gave **8** and **9** (Table 1).

***trans*-5-Methyl-4-phenyl-4,5-dihydro-1*H*,3*H*-azepin-2-one (8a)**: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.9 (d, ^3J(H,H) = 6.9 Hz, 3 H, CH_3), 2.6 (m, 1 H, CH), 2.7–3.0 (m, 3 H, CH, CH_2), 5.15 (dd, ^3J(H,H) = 9.9, ^3J(H,H) = 3.4 Hz, 1 H, CH), 5.85 (ddd, ^3J(H,H) = 9.9 Hz, ^3J(H,H) = 5.2, ^4J(H,H) = 1.7 Hz, 1 H, CH), 7.1–7.4 (m, 5 H, CH_{arom}), 7.55 (bs, 1 H, NH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 174.9 (s), 145.3 (s), 128.5 (d), 127.1 (d), 126.6 (d), 121.1 (d), 119.7 (d), 47.6 (d), 43.2 (t), 41.1 (d), 20.3 (q); HRMS (70 eV, EI): calcd for $C_{13}H_{15}NO$ (M^+) 201.1154, found 201.1157.

Methyl *syn*-4-methyl-6-oxo-3-phenylhexanoate (9): ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.85 (d, ^3J(H,H) = 6.9 Hz, 3 H, CH_3), 2.2 (m, 1 H, CH), 2.45 (m, 2 H, CH_2), 2.7 (m, 2 H, CH_2), 3.15 (m, 1 H, CH), 3.55 (s, 3 H, CH_3), 7.1–7.4 (m, 5 H, CH_{arom}), 9.7 (m, 1 H, CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 202.0 (d), 172.6 (s), 140.6 (s), 128.3 (d), 126.8 (d), 51.6 (q), 48.7 (t), 46.2 (d), 37.5 (t), 32.4 (d), 16.8 (q); HRMS (70 eV, EI): calcd for $C_{14}H_{17}O_3$ (M^+–1) 233.1178, found 233.1179.

1,7-Diphenyl-3-methoxy-(1*E*,3*E*,5*Z*)-4-azahepta-1,3,5-triene (10a): This compound was obtained in 25% yield along with azepine **7c**, as described above, by reaction of the oxime derived from cinnamaldehyde **6** (R^1 = Ph) and the corresponding (methoxy)cinnamyl carbene complex **2** (R^2 = Ph); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.7 (dd, ^3J(H,H) = 7.3, ^4J(H,H) = 1.3 Hz, 2 H, CH_2), 3.9 (s, 3 H, CH_3), 5.3 (dt, ^3J(H,H) = 7.7, ^3J(H,H) = 7.3 Hz, 1 H, CH), 6.8–7.6 (m, 13 H, 13 × CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 158.1 (s), 141.6 (s), 138.4 (d), 135.6 (s), 131.2 (d), 129.3 (d), 128.7 (d), 128.4 (d), 128.3 (d), 127.5 (d), 125.6 (d), 122.0 (d), 113.2 (d), 52.9 (q), 32.2 (t); HRMS (70 eV, EI): calcd for $C_{19}H_{19}NO$ (M^+) 277.1467, found 277.1463.

1-Methoxy-1-phenyl-(1*E*,3*Z*)-2-aza-1,3-hexadiene (10b): (Methoxybenzylidene)-pentacarbonylchromium (624 mg, 2 mmol) was added to a solution of oxime **6** derived from crotonaldehyde (R^1 = Me) (147 mg, 1 mmol) in THF (60 mL) at −40 °C. After 10 min the cold bath was removed, and the reaction stirred overnight at room temperature. Then, it was refluxed for 7 h and the resulting mixture cooled to room temperature, stirred with SiO_2 (5 g) for 3 h, and filtered. The residue was chromatographed on silica gel (hexane/AcOEt/NEt_3 10:1:1) affording 160 mg of imidate **10b** (85% yield); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.05 (t, ^3J(H,H) = 7.5 Hz, 3 H, CH_3), 2.45 (m, 2 H, CH_2), 3.9 (s, 3 H, CH_3), 5.0 (q, ^3J(H,H) = 7.5 Hz, 1 H, CH), 6.55 (d, ^3J(H,H) = 7.5 Hz, 1 H, CH), 7.3–7.5 (m, 5 H, CH_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 160.4 (s), 131.6 (s), 131.4 (d), 129.7 (d), 128.6 (d), 128.1 (d), 125.3 (d), 53.3 (q), 19.4 (t), 14.1 (q); HRMS (70 eV, EI): calcd for $C_{12}H_{15}NO$ (M^+) 189.1154, found 189.1157.

General procedure for the synthesis of azepines 12 and 13: A solution of carbene **11** (1 mmol), derived from (−)-menthol, $(CO)_5Cr{=}C(OMe)(Me)$ (500 mg, 2 mmol), and oxime **6a** (85 mg, 1 mmol) in THF (50 mL) was refluxed under nitrogen for 42 h. The resulting mixture was allowed to cool to room temperature, stirred with SiO_2 (3 g) for 3 h, and filtered over Celite. Removal of solvents under vacuum and column chromatography (SiO_2, hexane/AcOEt/NEt_3 20:1:1) furnished a 70:30 mixture of cycloadducts **12a,b** and **13a,b** (R* = (1*R*,2*S*,5*R*)-menthyl). A portion of the mixture (100 mg) was dissolved in hot MeOH (1 mL) and allowed to crystallize at −20 °C. The solid formed was filtered and washed with cold MeOH (this operation was repeated once) to give pure azepines **12a,b**. By starting with carbene **11** derived from (+)-menthol, a 30:70 mixture of cycloadducts **12c** and **13c** (R* = (1*S*,2*R*,5*S*)-menthyl) was obtained. Crystallization as above furnished pure azepine **13c**. Yields are given in Table 2.

(+)-(4*S*,5*R*)-2-(1*R*,2*S*,5*R*-Menthyl)-5-methyl-4-phenyl-4,5-dihydro-3*H*-azepine (12a): White solid. M.p. 107–108 °C; $[\alpha]_D^{20}$ = +159.5 (c = 0.19, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.7 (d, ^3J(H,H) = 6.9 Hz, 3 H, CH_3), 0.9 (d, ^3J(H,H) = 6.8 Hz, 3 H, CH_3), 0.9 (d, ^3J(H,H) = 6.8 Hz, 3 H, CH_3), 0.95 (d, ^3J(H,H) = 6.7 Hz, 3 H, CH_3), 0.9–1.2 (m, 2 H), 1.4 (m, 1 H), 1.5–1.8 (m, 4 H), 1.95 (m, 1 H), 2.25 (m, 1 H), 2.35 (dd, ^2J(H,H) = 12.9, ^3J(H,H) = 3.6 Hz, 1 H, CH_2), 2.6 (m, 1 H, CH), 2.9 (dd, ^2J(H,H) = 12.9, ^3J(H,H) = 6.9 Hz, 1 H, CH_2), 3.1 (m, 1 H, CH), 4.9 (dt, ^3J(H,H) = 10.7, ^3J (H,H) = 4.3 Hz, 1 H, CH), 5.3 (dd, ^3J(H,H) = 8.1, ^3J(H,H) = 5.1 Hz, 1 H, CH), 6.45 (dd, ^3J(H,H) = 8.1, ^4J(H,H) = 1.2 Hz, 1 H, CH), 7.2–7.4 (m, 5 H, CH_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 168.0 (s), 145.3 (s), 135.6 (d), 128.3 (d), 127.4 (d), 126.5 (d), 122.8 (d), 74.3 (d), 58.4 (d), 47.3 (d), 40.2 (t), 38.2 (d), 37.8 (t), 34.4 (t), 31.2 (d), 26.2 (d), 23.5 (t), 22.1 (q), 20.7 (q), 19.5 (q), 16.7 (q); HRMS (70 eV, EI): calcd for $C_{23}H_{33}NO$ (M^+) 339.2562, found 339.2558.

(+)-(4*S*,5*R*)-4-(2-Furyl)-2-(1*R*,2*S*,5*R*)-menthyl-5-methyl-4,5-dihydro-3*H*-azepine (12b): White solid. M.p. 83–84 °C; $[\alpha]_D^{20}$ = +295.8 (c = 0.59, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.8 (d, ^3J(H,H) = 6.9 Hz, 3 H, CH_3), 0.85 (d, ^3J(H,H) = 7.3 Hz, 3 H, CH_3), 0.9 (d, ^3J(H,H) = 6.9 Hz, 3 H, CH_3), 1.0 (d, ^3J(H,H) = 6.9 Hz, 3 H, CH_3), 0.8–1.1 (m, 2 H), 1.35 (m, 1 H), 1.45–1.7 (m, 4 H), 1.9 (m, 1 H), 2.2 (m, 1 H), 2.35 (dd, ^2J(H,H) = 12.9, ^3J(H,H) = 3.4 Hz, 1 H, CH_2), 2.6 (m, 1 H, CH), 2.85 (dd, ^2J(H,H) = 12.9, ^3J(H,H) = 6.9 Hz, 1 H, CH_2), 3.25 (m, 1 H, CH), 4.85 (dt, ^3J(H,H) = 10.7, ^3J(H,H) = 4.3 Hz, 1 H, CH), 5.2 (dd, ^3J(H,H) = 8.2, ^3J(H,H) = 5.2 Hz, 1 H, CH), 6.1 (m, 1 H, CH), 6.3 (m, 1 H, CH), 6.4 (dd, ^3J(H,H) = 8.2, ^4J(H,H) = 2.1 Hz, 1 H, CH), 7.3 (m, 1 H, CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 167.7 (s), 158.0 (s), 140.8 (d), 136.2 (d), 121.8 (d), 109.9 (d), 104.6 (d), 74.3 (d), 51.9 (d), 47.2 (d), 40.2 (t), 35.8 (t), 35.6 (d), 34.5 (t), 31.2 (d), 26.2 (d), 23.5 (t), 22.1 (q), 20.7 (q), 19.7 (q), 16.6 (q); HRMS (70 eV, EI): calcd for $C_{21}H_{31}NO_2$ (M^+) 329.2355, found 329.2354.

(−)-(4*R*,5*S*)-2-(1*S*,2*R*,5*S*-Menthyl)-5-methyl-4-phenyl-4,5-dihydro-3*H*-azepine (13c): White solid. M.p. 107–108 °C; $[\alpha]_D^{20}$ = −160.5 (c = 0.185, CH_2Cl_2). For the spectral data, see its enantiomer **12a**.

Hydrolysis of azepines 12a,b: *Method A*: A solution of azepines **12a,b** (0.5 mmol) in THF (30 mL) was mixed with 0.5 M HCl (30 mL) and stirred at room temperature for 1.5 h. The resulting mixture was diluted with water, extracted with diethyl ether (3 × 20 mL), and the combined organic layers dried over Na_2SO_4. The solvents were evaporated affording a mixture of chiral, nonracemic **8** and **14**, which were separated by column chromatography (SiO_2, hexane/AcOEt 2:1) affording pure **8** (32–34%) and **14** (59–63%).

Method B: A solution of azepines **12a,b** (0.5 mmol) in THF (30 mL) was mixed with 3 M HCl (30 mL) and stirred at room temperature for 1.5 h. Workup as above gave a mixture of **8** and **14** (<1:20), which yielded pure esters **14a,b** (90%) after column chromatography (SiO_2, hexane/AcOEt 2:1) (Table 3).

(−)-(4*S*,5*R*)-5-Methyl-4-phenyl-4,5-dihydro-1*H*,3*H*-azepin-2-one [(−)-8]: Colorless oil; $[\alpha]_D^{20}$ = −7.2 (c = 0.61, CH_2Cl_2). For the spectral data, see those given for racemic **8a**.

(+)-(4*S*,5*R*)-4-(2-Furyl)-5-methyl-4,5-dihydro-1*H*,3*H*-azepin-2-one (8b): Colorless oil; $[\alpha]_D^{20}$ = + 31.7 (c = 0.265, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.05 (d, ^3J(H,H) = 6.9 Hz, 3 H, CH_3), 2.7–2.9 (m, 3 H, CH, CH_2), 3.05 (m, 1 H, CH), 5.05 (dd, ^3J(H,H) = 9.9, ^3J(H,H) = 4.3 Hz, 1 H, CH), 5.8 (ddd, ^3J(H,H) = 9.9 Hz, ^3J(H,H) = 5.2, ^4J(H,H) = 1.7 Hz, 1 H, CH), 6.1 (m, 1 H, CH), 6.3 (m, 1 H, CH), 6.9 (bs, 1 H, NH), 7.35 (m, 1 H, CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 174.0 (s), 156.9 (s), 141.3 (d), 121.2 (d), 118.9 (d), 110.0 (d), 105.2 (d), 41.1 (d), 40.2 (t), 37.8 (d), 20.6 (q); HRMS (70 eV, EI): calcd for $C_{11}H_{13}NO_2$ (M^+) 191.0946, found 191.0947.

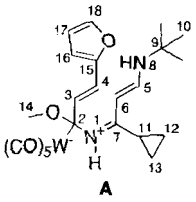
(−)-(1*R*,2*S*,5*R*)-Menthyl (3*R*,4*R*)-4-methyl-6-oxo-3-phenylhexanoate (14a): Colorless oil; $[\alpha]_D^{20}$ = − 41.3 (c = 0.155, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.45 (d, ^3J(H,H) = 6.9 Hz, 3 H, CH_3), 0.75 (d, ^3J(H,H) = 6.9 Hz, 3 H, CH_3), 0.85 (d, ^3J(H,H) = 6.5 Hz, 3 H, CH_3), 0.9 (d, ^3J(H,H) = 6.5 Hz, 3 H, CH_3), 0.7–1.0 (m, 3 H), 1.2 (m, 1 H), 1.3–1.5 (m, 2 H), 1.5–1.7 (m, 2 H), 1.75 (m, 1 H), 2.15 (m, 1 H), 2.4 (m, 2 H), 2.7 (m, 2 H), 3.1 (m, 1 H), 4.5 (dt, ^3J(H,H) = 10.7, ^3J(H,H) = 4.3 Hz, 1 H, CH), 7.1–7.4 (m, 5 H, CH_{arom}), 9.7 (m, 1 H, CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 202.0 (d), 171.7 (s), 140.6 (s), 128.4 (d), 128.1 (d), 126.7 (d), 74.0 (d), 48.8 (t), 46.7 (d), 46.6 (d), 40.6 (t), 38.2 (t), 34.1 (t), 32.6 (d), 31.2 (d), 25.7 (d), 23.0 (t), 21.9 (q), 20.6 (q), 16.9 (q), 15.8 (q); HRMS (70 eV, EI): calcd for $C_{23}H_{34}O_3$ (M^+) 358.2508, found 358.2505.

(−)-(1*R*,2*S*,5*R*)-Menthyl (3*R*,4*R*)-3-(2-furyl)-4-methyl-6-oxohexanoate (14b): Colorless oil; $[\alpha]_D^{20}$ = − 28.7 (c = 0.275, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.65 (d, ^3J(H,H) = 6.9 Hz, 3 H, CH_3), 0.8 (d, ^3J(H,H) = 6.9 Hz, 3 H, CH_3), 0.85 (d, ^3J(H,H) = 6.5 Hz, 3 H, CH_3), 0.9 (d, ^3J(H,H) = 6.8 Hz, 3 H, CH_3), 0.7–1.1 (m, 3 H), 1.3 (m, 2 H), 1.65 (m, 3 H), 1.85 (m, 1 H), 2.2 (m, 1 H), 2.4–2.8 (m, 4 H), 3.35 (m, 1 H), 4.6 (dt, ^3J(H,H) = 10.7, ^3J(H,H) = 4.3 Hz, 1 H, CH), 6.05 (m, 1 H, CH), 6.25 (m, 1 H, CH), 7.3 (m, 1 H, CH), 9.7 (m, 1 H, CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 201.9 (d), 171.4 (s), 154.5 (s), 141.4 (d), 109.9 (d), 106.9 (d), 74.3 (d), 48.9 (t), 46.8 (d), 40.6 (t), 39.8 (d), 36.0 (t), 34.1 (t), 31.2 (d), 25.9 (d), 23.1 (t), 21.9 (q), 20.7 (q), 16.2 (q), 15.9 (q); HRMS (70 eV, EI): calcd for $C_{21}H_{32}O_4$ (M^+) 348.2301, found 348.2297.

Reduction of ester derivative 14a: $LiAlH_4$ (76 mg, 2 mmol) was added in portions to a solution of **14a** (180 mg, 0.5 mmol) in THF (30 mL) at 0 °C and stirring continued at room temperature for 4 h. The resulting mixture was treated with methanol (2 mL) and then with 1 M NaOH, extracted with diethyl ether (3 × 20 mL), and dried over anhydrous sodium sulfate. Removal of solvents under reduced pressure and column chromatography (SiO_2, ethyl acetate) gave diol **15** (99 mg, 95% yield).

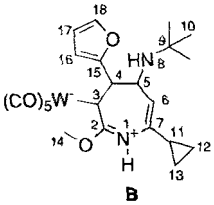
(−)-(3*R*,4*R*)-4-Methyl-3-phenyl-1,6-hexanediol (15): Colorless oil; $[\alpha]_D^{20}$ = − 9.6 (c = 0.595, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.8 (d, ^3J(H,H) = 6.9 Hz, 3 H, CH_3), 1.3 (m, 1 H), 1.75 (m 1 H), 2.0 (m, 5 H), 2.65 (m, 1 H), 3.4 (m, 1 H, CH_2), 3.5 (m, 1 H, CH_2), 3.65 (m, 1 H, CH_2), 3.75 (m, 1 H, CH_2), 7.1–7.4 (m, 5 H, CH_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 142.6 (s), 128.6 (d), 128.0 (d), 126.1 (d), 61.1 (t), 60.7 (t), 46.9 (d), 37.3 (t), 35.6 (t), 34.3 (d), 16.5 (q); HRMS: calcd for $C_{13}H_{20}O_2$ (M^+) 208.1463, found 208.1465.

Intermediates A–D and compound 3b:



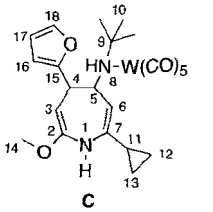
A

A: ^{1}H NMR (400.13 MHz, [D$_8$]THF, −80 °C, TMS): δ = 0.55–1.16 (m, 4H, H^{12} and H^{13}, 2 × CH$_2$), 1.25 (s, 9H, H^{10}, 3 × CH$_3$), 2.03 (m, 1H, H^{11}, CH), 2.84 (s, 3H, H^{14}, CH$_3$), 5.54 (d, ^3J(H,H) = 15.7 Hz, 1H, H^4, CH), 5.88 (d, ^3J(H,H) = 3.2 Hz, 1H, H^{16}, CH), 6.24 (dd, ^3J(H,H) = 1.8, 3.2 Hz, 1H, H^{17}, CH), 6.33 (d, ^3J(H,H) = 12.6 Hz, 1H, H^6, CH), 6.63 (d, ^3J(H,H) = 15.7 Hz, 1H, H^3, CH), 7.26 (d, ^3J(H,H) = 1.8 Hz, 1H, H^{18}, CH), 8.00 (dd, ^3J(H,H) = 12.6, 14.5 Hz, 1H, H^5, CH), 8.40 (brs, 1H, H^1, NH), 8.58 (bd, ^3J(H,H) = 14.5 Hz, 1H, H^8, NH); ^{13}C NMR (100.61 MHz, [D$_8$]THF, −80 °C, TMS): δ = 206.70 (s, CO), 204.72 (d, ^1J(C,W) = 131.5 Hz, 4 × CO), 166.51 (s, C^7), 156.35 (s, C^{15}), 150.08 (d, C^5), 142.21 (d, C^{18}), 139.20 (d, C^4), 113.05 (d, C^{17}), 106.09 (d, C^{16}), 103.48 (d, C^3), 102.70 (s, C^2), 96.53 (d, C^6), 55.70 (s, C^9), 50.75 (q, C^{14}), 30.46 (q, C^{10}), 15.04 (d, C^{11}), 9.23 and 7.76 (t, C^{12} and C^{13}); ^{15}N NMR (40.56 MHz, [D$_8$]THF, −90 °C, neat MeNO$_2$): δ = −204.9 (N^1), −228.7 (N^8); ^{183}W NMR (16.67 MHz, [D$_8$]THF, −80 °C, Na$_2$WO$_4$): δ = −3007.



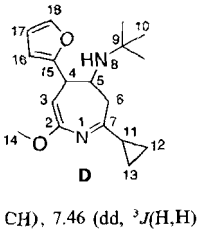
B

B: ^{1}H NMR (400.13 MHz, CD$_2$Cl$_2$, −80 °C, TMS): δ = 0.68 (s, 9H, H^{10}, 3 × CH$_3$), 1.85 (m, 1H, H^{11}, CH), 3.05 (ddd, ^3J(H,H) = 0.5 Hz, ^5J(H,H) = 0.8 Hz, ^2J(H,W) = 6.2 Hz, 1H, H^3, CH), 3.12 (ddd, ^3J(H,H) = 1.2 Hz, 5.0, 10.1 Hz, 1H, H^5, CH), 3.77 (s, 3H, H^{14}, CH$_3$), 4.12 (dd, ^3J(H,H) = 0.5, 10.1 Hz, H^4, CH), 5.31 (dd, ^3J(H,H) = 5.0 Hz, ^4J(H,H) = 1.2 Hz, 1H, H^6, CH), 6.20 (ddd, ^3J(H,H) = 3.1 Hz, ^4J(H,H) = 0.7 Hz, ^5J(H,H) = 0.8 Hz, 1H, H^{16}, CH), 6.27 (dd, ^3J(H,H) = 1.8, 3.1 Hz, 1H, H^{17}, CH), 7.35 (dd, ^3J(H,H) = 1.8 Hz, ^4J(H,H) = 0.7 Hz, 1H, H^{18}, CH); ^{13}C NMR (100.61 MHz, CD$_2$Cl$_2$, −80 °C, TMS): δ = 202.22 (s, CO), 200.4 (d, ^1J(C,W) = 129.9 Hz, 4 × CO), 176.36 (s, C^2), 155.37 (s, C^{15}), 142.29 (d, C^{18}), 134.53 (s, C^7), 127.93 (d, C^6), 109.86 (d, C^{17}), 108.05 (d, C^{16}), 57.97 (d, C^4), 56.40 (q, C^{14}), 52.78 (s, C^9), 52.75 (d, C^5), 29.0 (q, C^{10}), 26.23 (d, C^3); ^{15}N NMR (40.56 MHz, [D$_8$]THF, −90 °C, neat MeNO$_2$): δ = −252.4 (N^1); ^{183}W NMR (16.67 MHz, CD$_2$Cl$_2$, −80 °C, Na$_2$WO$_4$): δ = −2896.



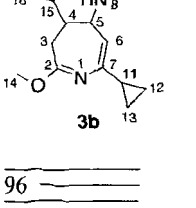
C

C: ^{1}H NMR (400.13 MHz, CD$_2$Cl$_2$, −80 °C, TMS): δ = 0.97 (s, 9H, H^{10}, 3 × CH$_3$), 1.57 (m, 1H, H^{11}, CH), 3.00 (d, ^2J(H,W) = 4.5 Hz, 1H, H^8, NH), 3.45 (dt, ^3J(H,H) = 2 × 1.7, 8.8 Hz, 1H, H^5, CH), 3.47 (s, 3H, H^{14}, CH$_3$), 3.64 (dd, ^3J(H,H) = 4.1, 8.8 Hz, 1H, H^4 CH), 3.84 (dd, ^3J(H,H) = 4.1 Hz, ^4J(H,H) = 2.3 Hz, 1H, H^3, CH), 4.35 (dd, ^3J(H,H) = 1.7 Hz, ^4J(H,H) = 2.8 Hz, 1H, H^6, CH), 5.41 (dd, ^4J(H,H) = 2.3, 2.8 Hz, 1H, H^1, NH), 6.37 (dd, ^3J(H,H) = 1.7, 3.1 Hz, 1H, H^{17}, CH), 6.47 (dd, ^3J(H,H) = 3.1 Hz, ^4J(H,H) = 0.7 Hz, 1H, H^{16}, CH), 7.45 (dd, ^3J(H,H) = 1.7 Hz, ^4J(H,H) = 0.7 Hz, 1H, H^{18}, CH); ^{13}C NMR (100.61 MHz, CD$_2$Cl$_2$, −70 °C, TMS): δ = 201.19 (s, CO), 197.93 (d, ^1J(C,W) = 127.3 Hz, 4 × CO), 153.36 (s, C^{15}), 152.89 (s, C^2), 142.76 (d, C^{18}), 135.23 (s, C^7), 110.62 (d, C^{16}), 109.78 (d, C^{17}), 105.37 (d, C^6), 75.16 (d, C^3), 58.18 (s, C^9), 56.86 (d, C^5), 55.68 (q, C^{14}), 38.89 (d, C^4), 30.00 (q, C^{10}), 17.88 (d, C^{11}); ^{15}N NMR (40.56 MHz, CD$_2$Cl$_2$, −80 °C, neat MeNO$_2$): δ = −319.8 (N^8), −276.0 (N^1); ^{183}W NMR (16.67 MHz, CD$_2$Cl$_2$, −80 °C, Na$_2$WO$_4$): δ = −2875.



D

D: ^{1}H NMR (400.13 MHz, [D$_8$]THF, −60 °C, TMS): δ = 0.62 (s, 9H, H^{10}, 3 × CH$_3$), 1.66 (d, ^2J(H,H) = 12.9 Hz, 1H, H^6, CH$_2$), 2.27 (dd, ^2J(H,H) = 12.9 Hz, ^3J(H,H) = 6.1 Hz, 1H, H^6, CH$_2$), 2.46 (m, 1H, H^{11}, CH), 2.55 (dd, ^3J(H,H) = 6.5, 12.3 Hz, 1H, H^4, CH), 3.35 (ddd, ^3J(H,H) = 1.9 Hz, 6.1, 12.3 Hz, 1H, H^5, CH), 3.59 (s, 3H, H^{14}), 4.80 (d, ^3J(H,H) = 6.5 Hz, 1H, H^3, CH), 6.23 (dd, ^3J(H,H) = 1.9, 3.4 Hz, 1H, H^{17}, CH), 6.24 (dd, ^3J(H,H) = 3.4 Hz, ^4J(H,H) = 0.7 Hz, 1H, H^{16}, CH), 7.46 (dd, ^3J(H,H) = 1.9 Hz, ^4J(H,H) = 0.7 Hz, 1H, H^{18}, CH); ^{13}C NMR (100.61 MHz, [D$_8$]THF, −60 °C, TMS): δ = 193.10 (s, C^7), 156.71 (s, C^2), 144.30 (s, C^{15}), 141.60 (d, C^{18}), 109.53 (d, C^{17}), 108.02 (d, C^{16}), 85.77 (s, C^3), 66.38 (d, C^5), 53.97 (q, C^{14}), 50.18 (s, C^9), 40.81 (d, C^4), 36.97 (t, C^6), 28.0 (q, C^{10}), 25.15 (d, C^{11}), 8.67 and 6.18 (t, C^{12} and C^{13}); ^{15}N NMR (40.56 MHz, [D$_8$]THF, −60 °C, neat MeNO$_2$): δ = −145.0 (N^1).



3b

3b: ^{1}H NMR (400.13 MHz, [D$_8$]THF −60 °C, TMS): δ = 0.78 (s, 9H, H^{10}, 3 × CH$_3$), 1.67 (m, 1H, H^{11}, CH), 2.65 (dd, ^2J(H,H) = 13.9 Hz, ^3J(H,H) = 1.2 Hz, 1H, H^3, CH$_2$), 2.77 (dd, ^2J(H,H) = 13.9 Hz, ^3J(H,H) = 7.8 Hz, 1H, H^3, CH$_2$), 3.27 (ddd, ^3J(H,H) = 1.2 Hz, 7.8, 12.0 Hz, 1H, H^4, CH), 3.35 (ddd, ^3J(H,H) = 0.9 Hz, 5.3, 12.0 Hz, 1H, H^5, CH), 3.42 (s, 3H, H^{14}, CH$_3$), 5.15 (dd, ^3J(H,H) = 5.3 Hz, ^4J(H,H) = 1.0 Hz, 1H, H^6, CH), 6.18 (dd, ^3J(H,H) = 3.1 Hz, ^4J(H,H) = 0.9 Hz, 1H, H^{16}, CH), 6.33 (dd, ^3J(H,H) = 1.9, 3.1 Hz, 1H, H^{17}, CH), 7.48 (dd, ^3J(H,H) = 0.9, 1.9 Hz, 1H, H^{18}, CH); ^{13}C NMR (100.61 MHz, [D$_8$]THF, −60 °C, TMS): δ = 175.65 (s, C^2), 153.83 (s, C^{15}), 148.26 (s, C^7), 141.54 (d, C^{18}), 120.16 (d, C^6), 109.96 (d, C^{17}), 106.51 (d, C^{16}), 56.41 (q, C^{14}), 51.84 (d, C^4), 50.44 (d, C^5), 49.95 (s, C^9), 29.35 (t, C^3), 28.73 (q, C^{10}), 15.44 (d, C^4), 8.98 and 6.48 (t, C^{12} and C^{13}); ^{15}N NMR (40.56 MHz, [D$_8$]THF, −60 °C, neat MeNO$_2$): δ = −185.4 (N^1).

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